PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4-32515A/626/627		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/05988	06.06.2003	10.06.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K45/06		
Applicant		
NOVARTIS AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2003	24.09.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Greif, G Telephone No. +49 89 2399-8659

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/05988

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-19 received on 18.08.2004 with letter of 17.08.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-5,7-19 (all in parts)

   because:

   ☒ the said international application, or the said claims Nos. 13 with respect to IA only relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-5,7-19 (all in parts)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-12,14-19 (claim 13 no opinion)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 13 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Claims 1-5 and 7-19 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved or in reference to a desirable characteristic, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result. (see also PCT/ISA/210, further information sheet).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Under Rule 66.1(e) PCT, a preliminary examination is not carried out on matter which has not been searched. Therefore, the preliminary examination has been carried out on the whole subject-matter of claim 6, and on the parts of claims 1-5 and 7-19 that have been searched.

2. Reference is made to the following documents:

   D1: WO 99/01124 A
   D2: WO 00/47584 A
   D3: US 2002/058286 A1
   D4: WO 01/64650 A
   D5: WO 01/81341 A
   D6: WO 01/81342 A
   D7: WO 01/72721 A

   D1 discloses compositions comprising a drug effective to reduce the growth of

multiresistant cells (epothilone), a cytotoxic agent and an anticancer agent (abstract; claims 1,3,4, 45-57).
D2 discloses compositions comprising epothilone derivatives, for the treatment of a variety of tumors, being used in combination with topoisomerase I or II inhibitors, microtubule active agent etc (abstract; p. 50-60).
D3 comprises compositions for the treatment of tumors comprising epothilones, in combination with other drugs such as topoisomerase II inhibitors, or microtubule active agents (p. 31-p.33, end of 3rd paragraph).
D4 discloses compositions for the treatment of cancer, comprising epothilone derivatives, and further active agents like adriamycin, vinblastin, or paclitaxel, for the treatment of cancers, also solide tumors (p. 74, lines 17-28, p. 78, lines 15-31, claims 1, 11, 28, 30, 33, 34).
D5 discloses pharmaceutical compositions comprising epothilones in combination with other active agents, such as topoisomerase I inhibitors or microtubule active agents, for the treatment of tumors (abstract; p. 63-64, claims 1, 2).
D6 discloses pharmaceutical composition comprising epothilone derivatives, in combination with other active compounds, such as topoisomerase I inhibitors or drugs interacting with microtubules (p. 53-54; claim 1).
D7 discloses methods for treating cancer with synergistic compositions comprising a cytotoxic agent like an epothilone, a topoisomerase inhibitor, an aromatase inhibitor, a HER antibody like trastuzumab. The treatment of solid tumors is also disclosed. (p. 23, line 36-p. 24, line 4; claims 1, 23-26,29,20).

3. Novelty
Since none of the cited documents discloses the particular epothilone derivative of formula (I) as claimed in the application, claims 1-19 are considered to be novel.

4. Inventive Step
D1 (or any of the documents disclosing the combined use of epothilones with another anticancer drug) is considered to be the closest prior art document, disclosing compositions for the treatment of cancer comprising combinations epothilones with agents like vinblastin or paclitaxel.
The difference between the claimed subject-matter and D1 consists of the particular epothilone derivative used.
The problem the present applications proposes to solve consists thus of proposing alternative combinations of drugs for the treatment of cancer.
The solution, the use of the particular epothilone in combination with a variety of

known drugs, is not considered inventive for the following reasons:
- The combination of drugs in cancer therapy is commonly known; furthermore, other specific compounds of the same class of drugs are used in therapy with other active agent. The expert in the field would therefore use the claimed compounds of formula (I) in combination with other drugs as taught by D1 with a reasonable expectation of success.
- There is nothing teaching away from using a compound of formula (I) in combination with other drugs of the same indication
- The application does not contain any data showing a specific beneficial effect of any claimed possibility of combination.
- In case the applicant would show an unexpected synergistic effect, the following has to be noted:
The applicant is furthermore reminded that synergistic effects are not predictable and are, per definition, unexpected. Therefore, even if the applicant would show a synergistic effect for a specific combination, considering the breath of the claims and the many possible compounds, this would not imply that other claimed combination for which no synergy has been shown, would be considered as involving an inventive step.
Claims 1-19 are thus not considered to be inventive.

5. Industrial applicability
For the assessment of the present claims 13 and 16-18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.